Influence of angiotensin converting enzyme inhibitors on stable myocardial ischemia in menopausal cardiac patients

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Summary

Purpose of Investigation:

Objective: The aim of the study was to investigate the influence of angiotensin converting enzyme inhibitor (Captopril) on stable demand ischemia in menopausal cardiac female patients.

Methods: In a prospective non-randomized evaluation of the effect of angiotensin converting enzymes inhibitors (ACE-I) (Captopril) on demand myocardial ischemia, 16 normotensive menopause female patients, mean age of 52 years with stable angina and known coronary artery disease (CAD) but normal left ventricular function, underwent a treadmill exercise test (Bruce Protocol), at baseline (T1) and one week following (50-75 mg) a daily dose of Captopril (CAPT2). Onset of symptoms, duration of exercise, magnitude of peak ST depression and homodynamic parameters were monitored.

Results: Captopril significantly increased the duration of exercise from (467 ± 169 to 536 ± 145 seconds, (p value < 0.02), but with increased peak of ST segment depression (from –1.4 ± 0.6 mm to -1.93 ± 1.2 mm, p value < 0.15). The double product remained unchanged (251 x 103 ± 55 in T1 and 248 x 103 ± 55 in CAPT2; the p value was < 0.8. All adverse effects on the treadmill were noted.

Conclusion: Although captopril tends to significantly effect prolongation of exercise time, there is no amelioration of the markers of ischemia.

Key words: Ace inhibitors; Stable angina, Menopause.

Introduction

Angiotensin converting enzyme inhibitors are the subject of a wide range of interest in cardiovascular disease. It has been suggested that Captopril decreases global myocardial oxygen consumption secondary to decreases in the heart rate-pressure product, without inducing reflex tachycardia [1-4]. Angiotensin converting enzyme inhibitors have also been demonstrated to exert a direct vasodilating effect on coronary blood flow together with an indirect effect via enhanced prostacycline synthesis [5-8]. Additionally, ACE inhibitors have a favorable action on post-infarction processes by limiting left ventricular dilatation [9-10] with attenuation of remodeling and perhaps slowing atherogenesis and thrombotic processes [11]. Despite this abundance of data, however, the role of ACE inhibitors (Captopril) on stable ischemia by testing the hypothesis that angiotensin converting enzyme inhibitors reduce myocardial ischemia in menopausal patients with stable angina remains controversial

Patients and Methods:

Sixteen normotensive and menopausal patients, mean age of 52 years (range 29-65 years), with stable angina and known coronary artery disease (Table 1) were identified. Ten patients had normal left ventricular contractility patterns, one had an inferior wall scar and five patients had antero-apical akinesis. Their angina had not increased in frequency or duration in the previous six months. All underwent a treadmill exercise test at baseline (T1) and one week following (50-75 mg) daily administration of Captopril (CAPT2). Patients were assessed by angina diaries and symptoms limited the treadmill exercise test using the Bruce Protocol of 3-minute stages. A 12-lead electrocardiogram was recorded before exercise, every minute during exercise and for five minutes after stopping.

Blood pressure was recorded non-invasively with a cuff, before exercise and every three minutes during exercise. The patients were asked to report on the onset of their angina, and its temporal course. Exercise was stopped for disabling angina or worsening S-T segment depression. The electrocardiograms were analyzed to determine heart rate and time to S-T segment depression (>1 mm). Before the test, all patients were kept on their regular antianginal therapy: calcium channel blockers, nitrates, ß-blockers and or in combination (Table 2). Resting and peak systolic and diastolic pressure before and after Captopril were registered. Total exercise time was also recorded with number of METs (metabolic equivalent) achieved at peak exercise pre and post Captopril. Peak S-T segment depression and double product (RPP × 100 before and after Captopril were also registered.

Consent was obtained from all patients before enrollment (Table 3).

Statistical Analysis:

Exercise parameters at baseline and post Captopril were compared and analyzed by the Student's t-test.

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Table 1. — *Coronary involvement in 16 patients.*

Coronary artery	Number of patients
Left anterior descending	10
Right coronary artery	2
Circumflex artery	2
2 vessels disease	3
3 vessels disease	0
Significant collaterals	6

Table 2. — *Anti-anginal therapy in 16 patients.*

Medications used	Patient nos.
Calcium channel blockers	1,2,3,5,6,7,8,9,10,12,13,14,16
Beta blockers	3,4,6,7,9,13,14,15,16
Nitrates	1,3,5,8,10,11
Antiplatelets	4,5,7,9,10,12,13,14,15,16

Results

All 16 patients completed the study with no complications. Four patients tolerated Captopril only at a dose of 12.5 mg, three times per day.

Hemodynamic Changes:

Systolic blood pressure at peak exercise dropped in eight patients, increased in four patients and remained unchanged in the remaining four patients. Peak mean systolic blood pressure at T1 was 117 mmHg while at CAPT2 it was 173 mmHg (statistically insignificant).

Resting diastolic pressure at T1 and CAPT2 was unchanged 82 ± 7 in T1 and 85 ± 11 in CAPT2 with a p value < 0.21. Peak exercise diastolic blood pressure was 76 ± 7 in T1 and 86 ± 7 in CAPT2 with a p value < 0.04. Heart rate at rest and at peak exercise was unaffected by Captopril (Table 4).

Table 3. — *Patient characteristics.*

Num	Age	/ Sex	Max. ST changes	Baseline			Peak exercise	Symptoms	Peak		
				EKG	HR	PB			HR	BP	%MPHR
1	65	F	V6 = -1.3	old anterolat M1	89	130/80	5.8METS 4:30	chest pain	131	140/70	84%
			V6 = -1.2	old anterolat M1	97	140/80	7.2METS 6:41	chest pain	138	150/80	90%
2	46	F	V4-6 = upslope 2.4	old anterolat M1	116	150/90	10.1METS 9:05	dyspnea	162	180/95	93%
			no change	old anterolat M1	112	150/90	11.3METS 10:14	dyspnea	172	180/80	98%
3	55	F	II,aVF,V5-6 = -2.1	normal	90	120/80	9.5METS 8:09	angina	139	180/80	84%
			II,aVF,V5-6 = -2.3	Ischemic	112	150/80	8.6METS 7:32	angina	148	180/90	90%
4	65	F	V5 = -1.2	normal	63	120/70	10.8METS 9:57	dyspnea	122	160/80	80%
			V5= -0.7	normal	59	110/70	10.1METS 9:11	dyspnea	118	130/80	76%
5	48	F	inf = -2.4, lat = -1.5	normal	84	160/90	5.1METS 3:55	angina	118	170/100	81%
			inf = -2.0, lat = -1.5	Ischemic	69	160/90	5.8METS 4:31	dizziness	112	160/90	68%
6	65	F	within normal	normal	75	130/90	10.1METS 9:00	fatigue	111	150/90	71%
			within normal	normal	76	160/90	10.9METS 10:00	fatigue	127	180/90	81%
7	63	F	V4-V5 = -1.5	normal	71	140/80	7.2METS 6:40	fatigue	121	190/70	77%
			V4-V5 = -0.5	Ischemic	82	140/80	7.3METS 6:45	fatigue	124	170/70	88%
8	41	F	within normal	normal	63	120/80	10.1METS 9:22	fatigue	156	210/60	87%
			within normal	normal	88	130/70	11.6METS 10:25	fatigue	153	200/90	85%
9	38	F	inf = -3.5, lat = --3.0	normal	76	130/90	7.4METS 6:46	EKG changes	170	170/90	93%
			inf = -3.0, lat = -3.5	Ischemic	93	130/80	10.1METS 9:00	same	184	170/100	101%
10	50	F	within normal	old inf.MI	60	140/80	12.7METS 11:08	none	166	180/100	97%
			within normal	old inf.MI	73	140/80	12.8METS 11:11	none	163	160/90	95%
11	49	F	within normal	old inf.MI	92	140/80	10.4METS 9:44	none	147	210/90	85%
			within normal	old inf.MI	89	140/80	10.5METS 9:46	none	136	190/90	79%
12	64	F	within normal	normal	71	150/90	11.5METS 10:23	fatigue	133	195/90	85%
			within normal	normal	80	140/85	13.4METS 12:30	fatigue	143	190/90	91%
13	57	F	within normal	normal	66	140/80	11.3METS 10:17	fatigue	148	210/90	90%
			within normal	normal	61	130/80	9.6METS 8:13	fatigue	127	170/80	77%
14	29	F	no change	old ant. M1	102	110/75	10.5METS 9:47	fatigue	172	170/80	90%
			no change	old ant. M1	100	130/90	13.4METS 10:01	fatigue	191	190/90	100%
15	60	F	inf + lat ischemia	atrial fib.	109	160/90	4.0METS 1:39	chest pain	160	180/95	100%
			inf + lat ischemia	sinus rythm	72	150/80	6.0METS 6:14	chest pain	128	180/80	80%
16	44	F	inf + lat ischemia	normal	97	120/70	5.5METS 4:18	chest pain	138	140/90	78%
			inf + lat ischemia	normal	75	120/60	7.9METS 7:08	chest pain	139	170/90	78%

Table 4. — *Hemodynamic changes.*

Hemodynamic changes	T1	CAP T2	P Value
Resting diastolic blood pressure	82 ± 7	85 ± 11	< 0.21
Peak exercise diastolic blood pressure	76 ± 7	86 ± 7	< 0.04
Duration of exercise (in seconds)	467 ± 169	536 ± 145	< 0.02
Peak S-T segment depression	−1.4 ± 0.6	−1.93 ± 1.2	< 0.15
Double product (RPP x 100)	251 × 10^3 ± 55	248 × 10^3 ± 55	< 0.8

Myocardial Ischemia:

For the whole group, total exercise duration (in seconds) increased from 467 ± 169 (in T1) to 536 ± 145 (in CAP T2); a p value of < 0.02 (Table 4).

Thirteen patients had improvement in the duration of exercise, but three patients decreased their exercise time. Peak S-T segment depression was -1.4 ± 0.6 mm in (T1) and -1.93 ± 1.2 in (CAP T2) with a p valve of < 0.15. The S-T segment depression worsened in six patients, improved in three patients and remained unchanged in seven patients [2, 4 and 8]. The double product in T1 was 250 x 10^3 ± 55 and 248 x 10^3 ± 55 (in CAPT2); p value < was 0.8 (Table 4).

Symptoms:

A few adverse reactions were detected during exercise: Dyspnea in two patients, angina in five, dizziness in one, fatigue in six, silent ischemia in one, and two patients were completely as symptomatic. The adverse effects of exercise exaggerated by Captopril were: dyspnea in one patient, worsening chest pain in four patients, fatigue in three patients, dizziness in one, but none experienced hypo tension (< 100 mmHg systolic). No symptomatic improvement was reported after Captopril use.

Discussion

There has been considerable recent interest in the use of angiotensin converting enzyme inhibitors for the modification of acute myocardial ischemia and remodeling of the left ventricle post-myocardial infarction. The use of ACE inhibitors in the context of chronic unstable angina is attractive because of theoretic effects on oxygen demand, as well as for potential stabilization of the plaque following the unanticipated demonstration of an anti-atherogenic effect [18]. The mechanisms of myocardial ischemia in stable angina are complex and are governed by hemodynamic and hydraulic factors, in addition to possible dynamic changes in the tone of vessel segments bearing atherosclerotic plaque. Changes in coronary pressure by diminishing the distending coronary pressure at the site of plaque stenosis could lead to collapse of the vessel, and therefore amplification of the severity of the stenosis. These observations have been collaborated by angiographic experimental findings by Gould [19] and others demonstrating quantitative changes in the lumen stenosis diameter following decrease of downstream perfusion pressure, and conversely increasing the lumen diameter stenosis by maintaining normal coronary pressure. The combination of calcium blockers and beta-blockers has been shown to be detrimental in many situations of chronic stable angina [20]. Similarly, the use of ACE inhibitors in the absence of hypertension and congestive heart failure could have a similar adverse hemodynamic-hydraulic effect secondary to a passive constriction at the site of mechanical stenosis. The findings of our study seem to support these theoretical considerations and are in agreement with numerous studies in the literature suggesting that in the absence of hypertension, the use of blood pressure lowering agents in chronic stable angina could be of minimal symptomatic or prognostic benefit and could actually be deleterious to some patients. The patients in the study were menopausal CAD ladies free of underlying hypertensive disease, and did not experience congestive heart failure. The extrapolation of this data to patients with hypertension and heart failure however should be made with extreme caution because the beneficial effects of angiotensin converting enzymes could outweigh a possible deleterious effect from systemic and coronary distal pressure changes. Clearly more information should be sought, in a larger series of patients before a final conclusion can be made.

Conclusion

The role of Captopril in demand ischemia is not predictable. Routine administration in menopausal, normotensive patients with stable angina does not seem justified.

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References

[1] Daly P., Rouleau J. L., Cousineau D. *et al.*: "Acute effects of Captopril on the coronary circulation of patients with hypertension and angina". *Am. J. Med.*, 1984, *76*, (suppl. 5B), 111, 5.

[2] Brunner D. B., Desponds G., Biollaz J. *et al.*: "Effect of a new angiotensin converting enzyme inhibitor MK421 and its lysine analogue on the components of the renin system in healthy subjects". *Br. J. Clin. Pharmacol.*, 1981, *11*, 461, 7.

[3] Graham T. P. Jr., Covell J. W., Sonnenblick E. H. *et al.*: "Control of myocardial oxygen consumption: relative influence of contractile state and tension development". *J. Clin. Invest.*, 1968, *47*, 375, 85.

[4] Daly P., Mettauer B., Rouleau J. L. *et al.*: " Lack of reflex increase in myocardial sympathetic tone after Captopril: Potential antianginal effect". *Circulation*, 1985, *71*, 317, 25.

[5] Fauter N. O., Holmes J. C.: "Coronary and myocardial actions of angiotensin". *Circ. Res.*, 1964, *14*, 191, 201.

[6] Lefer D. J., Lefer A. M.: "Coronary vascular actions of the converting enzyme inhibitor enalapril". *Proc. Soc. Exp. Biol. Med.*, 1984, *175*, 211, 4.

[7] Michel J. B., Dussaule J. C., Alhenc-Gelas F. *et al.*: "Can inhibition of the Renin-angiotensin system have a cardioprotective effect"? *J. Cardiovasc. Pharmacol.*, 1985, *7*, (suppl. 2), S75, 9.
[8] Wallis J. B., Borer J. S., Moses J. W. *et al.*: "The renin-angiotensin system: A primary factor in the control of coronary flow"? *Int. J. Cardiol.*, 1982, *2*, 263, 5.
[9] The SOLVD Investigators: "Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure". *N. Engl. J. Med.*, 1991, *325*, 293, 302.
[10] Pfeffer M. A., Braunwald E., Moye L. A. *et al.*: "Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators". *N. Eng. J. Med.*, 1992, *327*, 669, 77.
[11] Ridker P. M., Gaboury C. L., Conlin P. R. *et al.*: "Stimulation of plasminogen activator inhibitors in vivo by infusion of angiotensin II. Evidence of a potential interaction between the renin-angiotensin system and fibrinolytic function". *Circulation*, 1993, *87*, 1969, 73.
[12] Luu M., Stevenson W. G., Stevenson L. W. *et al.*: "Diverse mechanisms of unexpected cardiac arrest in advanced heart failure". *Circulation*, 1989, *80*, 1675, 80.
[13] Scroop G. C., Lowe R. D.: "Efferent pathways of cardiovascular response to vertebral artery infusions of angiotensin in the dog". *Clin. Sci.*, 1969, *37*, 605, 19.
[14] Lumbers E. R., McCloskey D. I., Potter E. K.: "Inhibition by angiotensin II of baroreceptor-evoked activity in cardiac vagal efferent nerves in the dog". *J. Physiol.*, 1979, *294*, 69, 80.
[15] Goldsmith S. R., Hasking G. J.: "Effect of a pressor infusion of angoiotensin II on sympathetic activity and heart rate in normal humans". *Circ. Res.*, 1991, *68*, 263, 8.
[16] Thurmann P., Odenthal H. J., Rietbrock N.: "Converting enzyme inhibition in coronary artery disease: a randomized, placebo-controlled trial with benazepril". *J. Cardiovasc. Pharmacol.*, 1991, *17*, 718, 23.
[17] Davies M. K.: "Effects of ACE inhibitors on coronary hemodynamics and angina pectoris". *Br. Heart. J.*, 1994, *72*, (suppl. 3), S52, 6.
[18] Simon J., Gibbs R., Crean P. A.: "The variable effects of angiotensin converting enzyme inhibition on myocardial ischemia in chronic stable angina". *Br. Heart. J.*, 1989, *62*, 112, 7.
[19] Gould K. L.: "Assessing coronary stenosis severity - a recurrent clinical need". *J. Am. Coll. Cardiol.*, 1986, *8*, 91, 94.
[20] Packer M.: "Drug therapy. Combined beta-adrenergic and calcium-entry blockade in angina pectoris". *N. Engl. J. Med.*, 1989, *320*, 709, 718.

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